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# SYNTHESIS CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL OF (1E)-1-((9-((4,5-DIHYDRO-5-THIOXO-1,3,4-OXADIAZOL-2-YL)METHYL)-9H-CARBAZOL-6-YL)METHYLENE)THIOSEMICARBAZIDE BEARING PHENYL THIAZOLE

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**Abstract:** The article is aimed to synthesize, characterize and screening the biological activity of (1E)-1-((9-((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-9H-carbazol-6-yl)methylene)thiosemicarbazide bearing phenyl thiazole
The structure of these newly synthesized compounds were characterised by $^{1}$H NMR,$^{13}$CNMR ,Mass ,IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar disc diffusion method

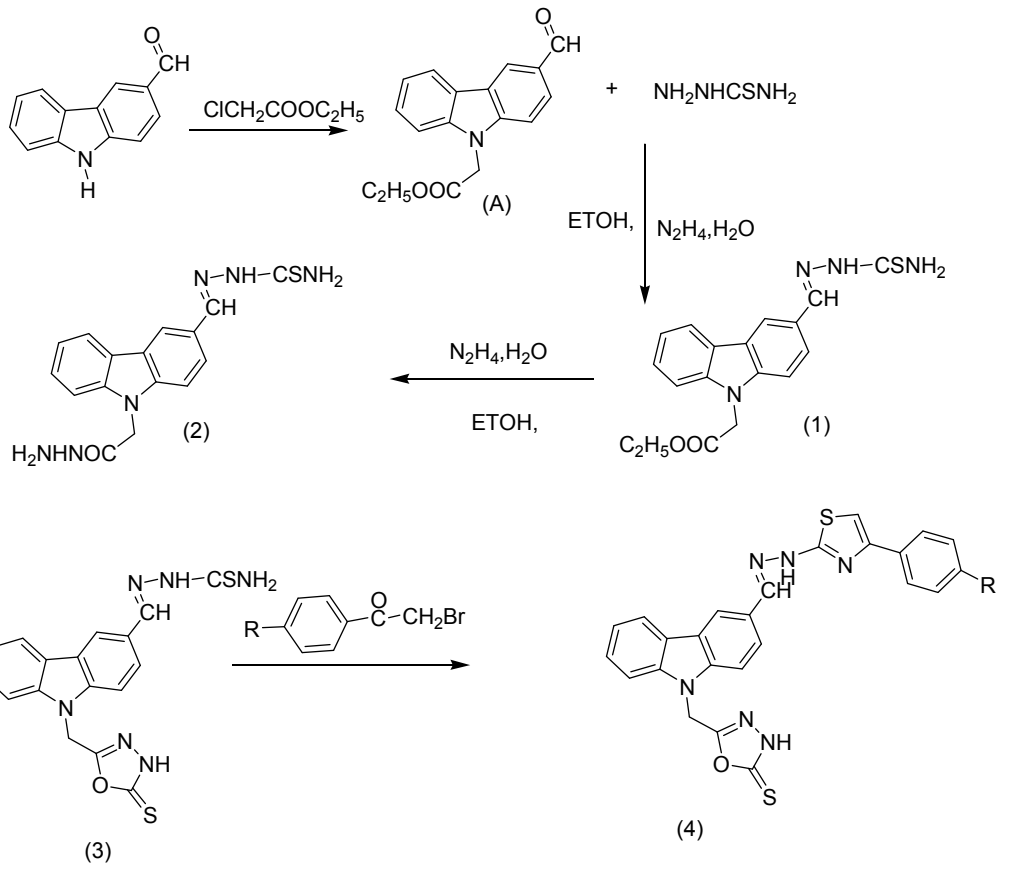
**Keywords:** Antibacterial activity, Antifungal activity, carbazole, thiazole.

## Introduction

Carbazole is considered a heterocyclic aromatic compound containing a tricyclic structure with two benzene rings fused on either side of the pyrrole ring. Carbazole is also considered a conjugated unit that possesses promising electronic and optical properties such as photoconductivity and photorefractivity. 1,2 Previous studies revealed that subsidiaries of carbazole have been additionally blended and applied in electronic devices such as organic light-emitting diodes (OLEDs). Although carbazole derivatives exhibit various applications in the field of material science, many carbazoles also possess diverse pharmacological properties 3 such as antibacterial,4 antifungal,5 antituberculosis, 6,7 antiproliferative,8 antiviral, 9 antitumor,10 antiinflammatory, 11 antioxidant,12 and antihistaminic 13 activities. Among the substituted carbazoles, 3-aminocarbazole plays a significant role in the field of medicinal chemistry, where it is applied as a versatile precursor for the synthesis of several bioactive annulated carbazole derivatives.14 3-Aminocarbazoles are also considered useful substrates in the synthesis of various dyes and pigments, stabilizers for polymers, pesticides, photographic materials, and diagnostic reagents in cytochemical studies. For instance, 3-amino-9-ethylcarbazole has been widely used as a peroxidase and considered suitable for the colorimetric detection of antibodies in the diagnosis of certain diseases. 15

## MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus .T.L.C. analysis were performed on precoated silicagel (E-Merck Kieselgel 60 $F_{254}$) plates and visualisation was done by exposing to iodine vapour .Solvent were purified by standard procedures before use .Column chromatography was conducted by using Silica gel with different solvent systems as elutes .IR Spectra were recorded in KBr on perkin –elmer spectrum BX series FTIR spectrometer. $^{1}$H-NMR spectrum were recorded on varian zemini 300MHz and 200MHz spectrometers using TMS as internal standard (chemical shifts in ppm). $^{13}$CNMR spectra were recorded on a brucker 75MHz spectrometer. Mass spectra were scanned on a varian MATCH -7 and jeol JMSD-300 mass spectrometer at 70 ev. Elemental analysis were carried out on carloerba 106 and perkin –analyser. All the chemicals used in the present investigation were purchased from Aldrich chemicals ;U.S.A.




| compd | 4(a) | 4(b) | 4(c) | 4(d) | 4(e) | 4(f) |
|---|---|---|---|---|---|---|
| R | -H | $-CH_3$ | $-OCH_3$ | -Cl | $-NO_2$ | $-CF_3$ |

**Synthesis of ethyl 2-(3-((E)-thiosemicarbazidomethyl)-9H-carbazol-9-yl)acetate(2):**
A solution of A (0.01mol) and hydrazine hydrate (0.015mol) in ethanol (20ml) was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered, washed with water and recrystalised from ethanol to afford **ethyl 2-(3-((E)-thiosemicarbazidomethyl)-9H-carbazol-9-yl)acetate**.
The IR(KBr) spectrum of this compound was recorded in the range 4000-667cm$^{-1}$ and the absorption signals were found at 3198(-NH), 3045(√-Ar-H)**,** 2975 and 2958 (√ aliphatic $CH_2$ and $CH_3$), 1755 (√ CO of ester group), 1640(C=N) , and 1195(√ C-O-C of ester group), 1170(C=S).
**$^1$HNMR Spectra ($\delta_{PPm}$ ):** The $^1$HNMR spectra of this compound was recorded in DMSO-$d_6$ solvent. The NMR signal of this compound was found at $\delta_{PPm,}$ 1.33 (t, 3H, J=13.2Hz, $CH_3$ of ethyl group), 4.11 (q, 2H, J=13.2Hz, $CH_2$ of ethyl group), 4.36 (s, 2H N-$CH_2$-C =O), 4.78(s, 2H, N-$CH_2$ group) ,4.95 (s,1 H,-N-NH) and 6.92 - 7.56 (m, 8H, carbazole nucleus), 11.19(s,1H,-NH), 14.7(s,1H,thiol-thione tautomeric proton SH).
**Synthesis of (1E)-1-((9-((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-9H-carbazol-6-yl)methylene)thiosemicarbazide** (3):
A mixture of 2 (19.9g,0.1mol), KOH(5.5g,0.1mol), ethanol(100ml) and carbon disulphide (6.02 ml,0.1mol) taken in a round bottomed flask fitted with a water cooled condenser was refluxed on a water bath till the evolution of hydrogen sulphide ceased. The excess of alcohol was removed by distillation. The reaction mixture was cooled to room temperature and the contents were poured to ice cold water and neutralized with dil.HCl. The solid precipitated was filtered, washed thoroughly with water and dried .The product was further purified by recrystallization from ethanol-dioxane mixture to give 3(a) yield 59%,m.p.229-230.

The IR(KBr) spectrum of this compound (3) was recorded in the range 4000-667cm$^{-1}$ and the absorption signals were found at 1626 (C=N),1180 (-C-O-C-),1156 (C=S),670(C-S-C),3185(-NH).
**$^1$HNMR Spectra ($\delta_{PPm}$ ):** The $^1$HNMR spectra of this compound was recorded in DMSO-$d_6$ solvent. The NMR signal of this compound was found at $\delta_{PPm,}$ 5.45 (s, 2H, -$CH_2$ thiaoxazole attached to carbazole ring), 7.08-8.35(complex m, 6H, four aryl protons of the indole ring, one α-proton of the carbazole ring,one aldehydimine proton), 7.20-8.28(complex m, 1H, one proton of the thiazolylring), 11.195 (s, 1H,-NH), 14.75 (s, 1H, thiol-thione tautomeric proton SH).
**5-((3-((2-(4-phenylthiazole-2-yl)hydrazono)methyl)-1H-indol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione(4):**
To a mixture of 3(a) (2.18 gr,) and $K_2CO_3$ (0.69gr,) in methanol (20ml) was added approximate α-halo ketones (chloroacetophenone , chloroacetone) 10ml and the mixture stirred at room temperature for 30min. At the end of this period, the solution was poured into ice cold water and neutralized with dil AcoH. The separated solid was filtered and dried to obtain crude. The crude compound obtained above was recrystalised from hot MeOH to obtain pure 4(a).
IR spectra : The IR(KBr) spectrum of 5-((3-((2-(4-phenylthiazole-2-yl)hydrazono)methyl)-1H-indol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione 4(a) was recorded in the range 4000-667cm$^{-1}$ and the absorption signals were found at, 1626 (C=N), 1180 (-C-O-C-), 1156 (C=S), 670(C-S-C), 3185(-NH),
NMR spectra : 5.42 (s, 2H, -$CH_2$ thiaoxazole attached to carbazole ring), 7.05-8.30 (complex, m, 9H, seven aryl protons of the carbazole ring, one α-proton of the carbazole ring, one aldehydimine proton), 7.18-8.26 (complex, m, 6H,one proton of the thiazolylring, five phenyl protons), 11.189 (s, 1H, -NH), 14.7 (s, 1H, thiol-thione tautomeric proton SH).

| COMPOUND | YIELD | M.P.O$^0$C | % of Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | | H | | N | |
| | | | Calcd | FOUND | Calcd | FOUND | Calcd | FOUND |
| 4a | 58% | 185 | 58.33 | 57.31 | 3.70 | 3.73 | 19.44 | 19.43 |
| 4b | 55% | 190 | 59.19 | 59.17 | 4.06 | 4.03 | 18.83 | 18.82 |
| 4c | 53% | 180 | 57.14 | 57.13 | 3.89 | 3.92 | 18.17 | 18.18 |
| 4d | 52% | 182 | 53.73 | 53.68 | 54.07 | 54.01 | 18.02 | 18.00 |
| 4e | 56% | 185 | 52.83 | 52.82 | 3.14 | 3.17 | 20.53 | 20.54 |
| 4f | 51% | 180 | 52.80 | 52.79 | 3.00 | 3.02 | 16.80 | 16.79 |

**Anti-Bacterial Activity:**

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcus aureus NCCS 2079 . The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of 250µglml and 500µglml using DMSO as a solvent, the Ciprofloxacin 10µglml disc was used as a standard .(Himedia, Laboratories Ltd, Mumbai).

The test results presented in the table -1,suggest that 4b,4d,4e exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

**Antifungal activity**

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of Penicillium and Trichophton.

Compounds were treated at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was Cyclopiroxolamine 50µglml against both organisms.The test results were presented in the table-2.

TABLE.- Antibacterial activity by disc diffusion method of carbazole linked thiazole. 4(a.f)

| Compound | Zone of inhibition (mm) | | | |
|---|---|---|---|---|
| | E.Coli | Staphylococcus | Klebsiella | Pseudomonas aeruginosa |
| 4a | 7.5(18) | 7.5(20) | 7.5(18) | 7.5(18) |
| 4b | 14(15) | 14(15) | 14(18) | 8(18) |
| 4c | 11(10) | - | - | 12.5(15) |
| 4d | 13(14) | - | 7.5(12) | - |
| 4e | 14(15) | - | 7.5(11) | - |
| 4f | 8(18) | 8(16) | 7.5(18) | - |
| Ciprofloxacin | 6.25(30) | 6.25(30) | 6.25(27) | 6.25(28) |

Table-;2 Antifungal activity by disc diffusion method for carbazole linked Thizole 4(a-f).

| Compound | Zone of inhibition (mm) | |
|---|---|---|
| | Penicillium | Trichophton |
| 4a | 7.5(18) | 7.5(18) |
| 4b | 13(15) | 13(11) |
| 4c | 13(10) | - |
| 4d | 13(15) | - |
| 4e | 13(12) | - |
| 4f | 7.5(16) | 7.5(18) |
| Cyclopiroxolamine | 7.5(27) | 3.12(30) |

**Conclusions:**

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The thiazole showed better antibacterial and antifungal activities.
3. Thiazoles and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

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